REMARKS

Claims 1-54 were pending in the instant application. Claims 29-54 are under active consideration. Claims 1-28 have been canceled without prejudice to Applicants' rights to pursue the subject matter for claims 1-28 in one or more related applications. Claims 49-51 have been rewritten in independent format in view of the cancellation of claims 1-28. New claims 55 and 56 have been added. Support for claim 55 can be found in the specification at page 36, lines 30-32. Support for new claim 56 can be found in the specification, for example at page 34, lines 23-24. No new matter is added. For the Examiner's convenience, a marked up copy of the amended claims is attached hereto as Exhibit A, and copy of the claims as will be pending upon entry of the amendments made herein is attached hereto as Exhibit B.

The Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 41 and 49-54 are rejected under 35 U.S.C. § 112, second paragraph, allegedly as being indefinite for failing to point out and distinctly claim the subject matter claimed as the invention.

Specifically, the Examiner contends that claim 41 is indefinite as it lacks antecedent support for "Signal Domain." Applicants respectfully disagree; claim 41 depends from claim 29 which describes the Signal Domain as being created by extending the second nucleic acid with a DNA polymerase in the presence of a labeled nucleotide and which shows complementarity toward and is hybridizable to the Signal Template Domain (see page 44, lines 13-16 of the instant specification). Therefore, the recitation of "Signal Domain" in claim 41 has antecedent basis and, accordingly, the rejection of claim 41 under 35 U.S.C. § 112, second paragraph, should be withdrawn.

Claims 49, 50 and 51 are rejected under 35 U.S.C. § 112, second paragraph, because they depend from canceled claims. Claims 52-54 are also rejected under 35 U.S.C. § 112, second paragraph because these claims depend from claim 51. In response, Applicants have amended claims 49, 50 and 51 to be independent claims. Thus, the rejection of claims 49-54 under 35 U.S.C. § 112, second paragraph, has been obviated and should be withdrawn.

The Rejections Under 35 U.S.C. § 102(e) Should be Withdrawn

Claims 29, 30, 32, 33, 40 and 44 are rejected as being anticipated under 35 U.S.C. § 102(e) by Shuber, U.S. Patent 5,882,856 ("Shuber"). Applicants do not agree. In view of the remarks below, Shuber does not anticipate the claimed invention.

The Examiner states that Shuber "discloses the use of a chimeric primer that is described as being configured 5'-XY-3'. " The Examiner states that "the "X" domain meets the limitations of the Applicants' "Signal Template Domain" and the "Y" domain meets the limitations of the Substrate hybridization domain of the "first sequence" (the first nucleic acid; page 14, line 10). Applicants respectfully disagree. In the chimeric primer of Shuber, the 5' end of the primer does not hybridize to the target sequence of interest, whereas the 3' end of the primer does hybridize to the target sequence of interest. Therefore, the 3' end of the Shuber primer serves as a primer for amplification of the target sequence of interest, which serves as a template for the amplification reaction. In contrast, the first nucleic acid of the presently claimed invention, comprising a Signal Template Domain and the Substrate Hybridization Domain, serves as a template for an extension reaction with a DNA polymerase. The first sequence is, in fact, designated the "Template Nucleic Acid" (page 14, line 10).

In contrast to Shuber, the actual primer in presently claimed methods is the "second nucleic acid" (the Substrate Nucleic Acid; page 14, line 23-24). The Examiner contends, however, that the second nucleic acid meets the limitation of Shuber's target, which serves as a template in Shuber's DNA amplification reaction. Applicants respectfully disagree. Shuber's target DNA preferably "represents a sample of genomic DNA isolated from a patient" (column 5, lines 25-26). In contrast, Applicants' second nucleic acid, which comprises a Template Hybridization Domain and a Target Binding Domain, is a chimeric oligonucleotide whose 5' end, the Target Binding Domain, hybridizes to a target of interest and whose 3' is complementary to the Substrate Hybridization Domain. Not only does Applicants' second nucleic acid differ from that of Shuber in structure, as discussed above, it also differs in function. Particularly, while Shuber's target serves as a template in Shuber's amplification reaction, Applicants' second nucleic acid serves as a primer in a primer extension reaction.

Not only does Shuber not teach the compositions used in the present invention, as discussed above, Shuber also does not teach the methods of the present invention. Specifically, Shuber discloses the use of the 5'-XY-3' as a primer for simultaneous amplification of multiple target DNA sequences in a single PCR, using a thermostable polymerase (Taq). Also provided are methods for amplification for a variety of target DNA sequences using these primers. Shuber does not teach the use of labeled nucleotides or the use of a variety of DNA polymerases during an extension reaction, let alone doing so with Applicants' first and second nucleic acids. Moreover, Shuber does not teach the use of a labeling reaction with a Substrate Nucleic Acid and a Template Nucleic Acid to generate probes with high specific activity or the use of probes generated using this method for the detection of target sequences.

In view of the foregoing, Applicants respectfully submit that Shuber does not anticipate the presently claimed invention. Accordingly, Applicants respectfully assert that the rejection of claims 29, 30, 32, 33, 40, and 44 under 35 U.S.C. § 102(e) over Shuber should be withdrawn.

The Rejections Under 35 U.S.C. § 103(a) Should be Withdrawn

Claims 31, 35-38, 41-43, 45-47 and 48 have been rejected by the Examiner for obviousness under 35 U.S.C. § 103(a). Applicants respectfully disagree with the Examiner's rejections and submit that the rejections should be withdrawn for the reasons discussed below.

A finding of obviousness under 35 U.S.C. § 103 requires a determination of the scope and the content of the prior art, the differences between the invention and the prior art, the level of the ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 U.S. 1 (1966). The relevant inquiry is whether the prior art suggests the invention, and whether one of ordinary skill in the art would have had a reasonable expectation that the claimed invention would be successful. In re Vaeck, 947 F.2d 488, 20 U.S.P.Q. 2d 1438 (Fed. Cir. 1991). Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. In re Dow Chemical Co., 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988).

The present invention provides methods and kits whereby labeled nucleic acids of high specific activity can be produced for the subsequent detection of target nucleic acids. Claims 29-54 as pending provide such methods and kits for the labeling of nucleic acids.

Claim 31 is rejected under 35 U.S.C. § 103(a) over Shuber in view of Khan *et al.*, U.S. Patent 6,248,548 ("Khan"). The Examiner states that Khan discloses that "suitable templates include DNA as well as RNA" and that it would have "been obvious to one of ordinary skill in the art to have modified the method of Shuber whereby RNA was used as a template and to have used a RNA dependent DNA polymerase so as to generate cDNA runoffs" since these would be more resistant to degradation.

As discussed above, Shuber does not suggest, much less teach the method of this invention, that of hybridizing a Substrate Nucleic Acid and a Template Nucleic Acid and then extending the Substrate Nucleic Acid in a primer extension reaction in the presence of labeled dNTPs to generate a probe of high specific activity. Khan does not remedy the deficiencies of Shuber. Khan discloses the propargylethoxyamino nucleosides and primer extension methods in DNA sequencing, PCR and primer extension reactions. Khan, like Shuber, does not provide a hint or suggestion of, or the use of a primer extension reaction that employs a Substrate Nucleic Acid and a Template Nucleic Acid using labeled nucleotides in a polymerase reaction for making high specific activity probes. Accordingly, claim 31 is not obvious over Shuber in view of Khan.

Claims 35-38, 41-43 and 48 have been rejected under 35 U.S.C. § 103(a) as being obvious over Shuber in view of Grossman *et al.*, U.S. Patent 5,989,871 ("Grossman") and Khan. The Examiner states that Grossman discloses "the generation of homopolymeric tails" and "the use of a detectable nucleotide, e.g., a fluorophore". The Examiner also notes that Khan discloses "a plethora of labels that can be used in primer extension reactions." The Examiner thus concludes that it would have been obvious to one having ordinary skill in the art at the time the invention was made to incorporate any of the labels disclosed by Khan or Grossman into the primer extension product of Shuber. The Examiner further alleges that it would have been obvious to have incorporated the use of a chain terminating nucleotide into a specific sequence so as to limit the amount and direction of any extension reaction.

Grossman does not remedy the deficiencies of Shuber or Khan, alone or in combination. Grossman discloses methods and compositions for detecting target polynucleotide regions, by, *inter alia*, hybridizing the target polynucleotide regions to probe oligonucleotides comprising a target-complementary regions, and labeling the target-probe complex with a polymer alters the charge/translational frictional draft of the hybrid nucleic acid. Following hybridization of sequence-specific probes to their targets, the probes are modified, *inter alia*, by homopolymeric tailing of the probe fragments. Thus, like Khan, Grossman does not provide a hint or suggestion of, or the use of, the high specific activity probes of the present invention or making such probes according to the instantly claimed methods. Moreover, as discussed below, Grossman teaches homopolymeric tailing that is distinct from the homopolymer structures of the present invention. The skilled artisan would recognize that homopolymer tailing, as described in Grossman, is a method whereby homopolymeric tails are added to a preexisting molecule using terminal transferase to catalyze the addition of the nucleotides to it; this enzyme does not use a template for the reaction, as discussed in the specification for example at pages 2-3. In contrast, the homopolymers of the present invention are a result of a template based DNA polymerase catalyzed reaction. Accordingly, Grossman does not remedy the deficiencies of Shuber and/or Khan.

Claims 45-47 are rejected, allegedly as being obvious over Shuber in view of Brown, WO 93/05175 ("Brown"). Brown discloses the use of 2,6- diaminopurine in oligonucleotides, and the Examiner states that it would have been obvious to have incorporated 2,6-diaminopurine into the sequences of Shuber.

Applicants respectfully disagree. Brown does not remedy the deficiencies of Shuber, Khan and Grossman, alone or in combination. Brown discloses oligonucleotides comprising base analogues which include 2,6-diaminopurine and the use of these oligonucleotides in PCR and nucleic acid hybridization. However, Brown does not contemplate the use of a Template Nucleic Acid and a Substrate Nucleic Acid to generate a high specificity probe, let alone the use of base analogues such as 2,6-diaminopurine in such methods. Thus, Brown does not teach or suggest the current invention, alone or in combination with Shuber, Khan, and/or Grossman.

Applicants further submit that the Examiner is employing, perhaps unconsciously, impermissible hindsight reconstruction based on knowledge of Applicants' invention to make his alleged *prima facie* case of obviousness. Such hindsight reconstruction does not meet the legal standard for obviousness:

> It is error to reconstruct the patentee's claimed invention from the prior art by using the patentee's claim as a "blueprint". When prior art references require selective combination to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight obtained from the invention itself.

Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir 1985).

Both the suggestion of the claimed invention and the expectation of success must be in the prior art, not in the disclosure of the claimed invention. In re Dow Chemical Co., 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir 1988). There are no explicit or implicit suggestions in Shuber, Khan, Grossman or Brown, alone or in combination, to practice the claimed methods and kits of the presently claimed invention, that of labeling probes to a high specific activity and the use of the probes to detect target sequences. "Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." Carella v. Starlight Archery, 804 F.2d 135, 231 USPQ 644 (Fed. Cir. 1986).

In view of the foregoing, Applicants respectfully submit that the rejection under 35 U.S.C. § 103 (a) of the pending claims has been obviated and should be withdrawn.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application. All pending claims (29-56) fully meet all statutory requirements for patentability. Withdrawal of the Examiner's rejections and early allowance and action for issuance are respectfully requested.

Applicants respectfully request that the Examiner call the undersigned attorney at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date: January 18, 2002

Jennifer Gordon 30,753
Jennifer Gordon (Reg. No.)

By: Muna Abu-Shaar
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Limited Recognition Under 37 C.F.R. § 10.9(b)
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Enclosures

EXHIBIT A
U.S. Application No. 09/497,943
Marked Up Version of Amended Claims

49. (Amended) A method for detecting a Target Nucleic Acid in a sample, comprising:

a. contacting the sample with [the] a Complex [of claim 1] under conditions whereby said Complex can bind to the Target Nucleic Acid to form a Complex-Target Nucleic Acid hybrid, wherein said Complex comprises:

i. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

(1) the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

(2) the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

ii. a second nucleic acid comprising from 3' to 5': a Signal Domain, a Template Hybridization Domain and a Target Binding Domain, wherein:

(1) the Signal Domain comprises a sequence of about 5 to about 100 nucleotides, which sequence shows complementarity toward and is hybridizable to the Signal Template Domain of the first nucleic acid, and of which at least two nucleotides are detectably labeled;

(2) the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

(3) the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

and

b. detecting any Complex-Target Nucleic Acid hybrids, so that if a Complex-Target Nucleic Acid hybrid is detected, a Target Nucleic Acid is detected in the sample.

50. (Amended) A method for detecting a Target Nucleic Acid in a sample, comprising:

a. dissociating [the] a Complex [of claim 1] to generate a single stranded first nucleic acid and a single stranded second nucleic acid, wherein said complex comprises:

i. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

(1) the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

(2) the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

ii. a second nucleic acid comprising from 3' to 5': a Signal Domain, a Template Hybridization Domain and a Target Binding Domain, wherein:

(1) the Signal Domain comprises a sequence of about 5 to about 100 nucleotides, which sequence shows complementarity toward and is hybridizable to the Signal Template Domain of the first nucleic acid, and of which at least two nucleotides are detectably labeled;

(2) the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

(3) the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

b. contacting the sample with the second nucleic acid of step a. under conditions whereby said second nucleic acid can bind to the Target Nucleic Acid to form a second nucleic acid-Target Nucleic Acid hybrid; and

c. detecting any second nucleic acid-Target Nucleic Acid hybrids, so that if a second nucleic acid-Target Nucleic Acid hybrid is detected, a Target Nucleic Acid is detected in the sample.

51. (Amended) A kit for labeling a nucleic acid molecule, comprising [the] a reaction mixture [of claim 15,] and a DNA polymerase, wherein the reaction mixture comprises:

a. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

i. the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

ii. the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

b. a second nucleic acid comprising from 3' to 5':a Template Hybridization Domain and a Target Binding Domain, wherein:

i. the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

ii. the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain.

EXHIBIT B
U.S. Application No. 09/497,943
Claims as Pending Following Entry of Amendments Made Herein

29. (Amended) A method of labeling a nucleic acid molecule, comprising the steps of:

a. Hybridizing a first nucleic acid to a second nucleic acid, wherein the first nucleic acid comprises, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

i. the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

ii. the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and the second nucleic acid comprises from 3' to 5': a Template Hybridization Domain and a Target Binding Domain, wherein:

i. the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

ii. the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

and:

b. extending the second nucleic acid with a DNA polymerase in the presence of a labeled nucleotide to create a Signal Domain having a sequence which shows complementarity toward and is hybridizable to the Signal Template Domain, thereby labeling said second nucleic acid molecule.

30. The method of claim 29, wherein the nucleotides which comprise the first or second nucleic acid are deoxyribonucleotides.

31. The method of claim 29, wherein the nucleotides which comprise the first or second nucleic acid are ribonucleotides.

32. The method of claim 29, wherein the second nucleic acid consists of about 15 to about 150 nucleotides.

33. The method of claim 29, wherein the Substrate Hybridization Domain is at the 3' end of the first nucleic acid.

34. The method of claim 29, wherein the Substrate Hybridization Domain comprises a sequence of about 5 to about 10 nucleotides.

35. The method of claim 29, wherein the Substrate Hybridization Domain cannot be extended by a 5'→3' DNA polymerase.

36. The method of claim 35, wherein the Substrate Hybridization Domain further comprises an extension of nucleotides at the 3' end of said Substrate Hybridization Domain, the extension having no complementarity to the Template Hybridization Domain of the second nucleic acid.

37. The method of claim 35, wherein the Substrate Hybridization Domain comprises a 3'-terminal modified nucleotide.

38. The method of claim 37, wherein the modification is selected from the group consisting of: a 3'-amino-modifier, a 2', 3'-dideoxynucleotide, a 3'-phosphate, and a modified 3'-phosphate group.

39. The method of claim 29, wherein the Substrate Hybridization Domain comprises at least one one nucleotide which comprises a modified cytidine, which nucleotide is selected from the group consisting of: C5-methyl-dC and C5-propynyl-dC.

40. The method of claim 29, wherein the Signal Template Domain comprises a sequence of about 10 to about 50 nucleotides.

41. The method of claim 29, wherein the Signal Domain is at least 50%, at least 70%, at least 90% or 100% homopolymeric.

42. The method of claim 29, wherein at least 60%, at least 80% or 100% of the nucleotides of the Template Hybridization Domain comprise guanosine or cytidine or a combination thereof.

43. The method of claim 29, wherein at least 60% of the nucleotides of the Template Hybridization Domain comprise guanosine or cytidine or a combination thereof, and the Signal Domain is at least 50% homopolymeric.

44. The method of claim 29, wherein the extending step is carried out by a DNA polymerase selected from the group consisting of: *E. coli* DNA polymerase I holoenzyme, Klenow fragment of *E. coli* DNA polymerase I, T4 DNA polymerase, T7 DNA polymerase, and a DNA polymerase encoded by a thermophilic bacterium.

45. The method of claim 29, wherein the Template Hybridization Domain or the Substrate Hybridization Domain comprises at least one modified nucleotide, which modified nucleotide increases the hybridization affinity of said Template Hybridization Domain to said Substrate Hybridization Domain.

46. The method of claim 45, wherein at least one modified nucleotide is found in the Template Hybridization Domain.

47. The method of claim 46, wherein at least one modified nucleotide is selected from the group consisting of: C5-methyl-dC, C5-propynyl-dC, C5-propynyl-dU, and 2, 6-diaminopurine.

48. The method of claim 29, wherein at least one nucleotide comprises a label selected from the group consisting of: ^{32}P, ^{33}P, ^{35}S, fluorescein, digoxigenin, biotin, Cy5, Cy3, and rhodamine.

49. (Amended) A method for detecting a Target Nucleic Acid in a sample, comprising:

a. contacting the sample with a Complex under conditions whereby said Complex can bind to the Target Nucleic Acid to form a Complex-Target Nucleic Acid hybrid, wherein said Complex comprises:

i. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

(1) the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

(2) the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

ii. a second nucleic acid comprising from 3' to 5': a Signal Domain, a Template Hybridization Domain and a Target Binding Domain, wherein:

(1) the Signal Domain comprises a sequence of about 5 to about 100 nucleotides, which sequence shows complementarity toward and is hybridizable to the Signal Template Domain of the first nucleic acid, and of which at least two nucleotides are detectably labeled;

(2) the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

(3) the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

and

b. detecting any Complex-Target Nucleic Acid hybrids, so that if a Complex-Target Nucleic Acid hybrid is detected, a Target Nucleic Acid is detected in the sample.

50. (Amended) A method for detecting a Target Nucleic Acid in a sample, comprising:

a. dissociating a Complex to generate a single stranded first nucleic acid and a single stranded second nucleic acid, wherein said complex comprises:

i. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

(1) the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

(2) the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

ii. a second nucleic acid comprising from 3' to 5': a Signal Domain, a Template Hybridization Domain and a Target Binding Domain, wherein:

(1) the Signal Domain comprises a sequence of about 5 to about 100 nucleotides, which sequence shows complementarity toward and is hybridizable to the Signal Template Domain of the first nucleic acid, and of which at least two nucleotides are detectably labeled;

(2) the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

(3) the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain;

b. contacting the sample with the second nucleic acid of step a. under conditions whereby said second nucleic acid can bind to the Target Nucleic Acid to form a second nucleic acid-Target Nucleic Acid hybrid; and

c. detecting any second nucleic acid-Target Nucleic Acid hybrids, so that if a second nucleic acid-Target Nucleic Acid hybrid is detected, a Target Nucleic Acid is detected in the sample.

51. (Amended) A kit for labeling a nucleic acid molecule, comprising a reaction mixture and a DNA polymerase, wherein the reaction mixture comprises:

a. a first nucleic acid comprising, from 3' to 5': a Substrate Hybridization Domain and a Signal Template Domain, wherein:

i. the Substrate Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides; and

ii. the Signal Template Domain comprises a sequence of about 5 to about 100 nucleotides;

and:

b. a second nucleic acid comprising from 3' to 5':a Template Hybridization Domain and a Target Binding Domain, wherein:

i. the Template Hybridization Domain comprises a sequence of about 5 to about 20 nucleotides, is not detectably labeled, and shows complementarity toward and is hybridizable to the Substrate Hybridization Domain of the first nucleic acid;

ii. the Target Binding Domain is not detectably labeled and comprises a nucleotide sequence heterologous to that of the Template Hybridization Domain.

52. The kit of claim 51, wherein at least 60% of the nucleotides of the Template Hybridization Domain comprise guanosine or cytidine or a combination thereof, and the Signal Domain is at least 50% homopolymeric.

53. The kit of claim 51, wherein the Substrate Hybridization Domain comprises a predetermined sequence comprising CCCGCC and the Signal Template Domain comprises a predetermined sequence comprising TTTTTTTTTT.

54. The kit of claim 51, wherein, the first nucleic acid comprises a predetermined sequence comprising SEQ ID NO:10.

55. (New) The method of claim 29, wherein the Probe has a specific activity of at least 7 x 10^7 CPM per picomole, and wherein the Probe comprises the Target Binding Domain, the Template Hybridization Domain and the Signal Domain.

56. (New) The method of claim 29, wherein the Probe has a specific activity of at least 9 x 10^7 CPM per picomole, and wherein the Probe comprises the Target Binding Domain, the Template Hybridization Domain and the Signal Domain.